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The Role of Methotrexate in Psoriatic Therapy in the Age of Biologic and Biosimilar Medication: Therapeutic Benefits versus Toxicology Emergencies

Carolina Negrei and Daniel Boda

Additional information is available at the end of the chapter

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Abstract

Used in the psoriasis therapy for over 30 years, methotrexate belongs to the non-biological medication class. Its continued use must be studied in the context of the modern unprecedented powerful pharmacological and medical development, due to the particularly, even uniquely fast development of biologicals, which assume an extremely important role in cutting-edge medicine. This status has turned biosimilars and all related matters into an outstanding challenge not only for researchers worldwide but also for other medicinal product-associated fields such as development of regulatory standards and pharmacovigilance, to mention the most important. However, against a comparable high-risk background, compounded by the additional danger of serious cumulative toxicity, methotrexate therapy continues to be recommended mainly for patients suffering from severe psoriasis, seriously affecting their quality of life.

Keywords: methotrexate, biosimilars, psoriasis, benefit, toxicology

1. Introduction

Known since ancient times (judging by descriptions of typical lesions found in mummified bodies, as early as the Christian era), psoriasis is a frequent autoimmune disease mostly causing chronic inflammation of the skin, through other manifestations are not uncommon. Psoriasis is mediated by T-cells and as such is the more frequently encountered human disease of its class. Since the very beginning and as far as the late Middle Ages, because of its mistaken diagnosis as

leprosy and subsequent isolation of patients, it was accompanied by significant social and economic burden. Further in history, at the beginning of the nineteenth century, scientists finally observed and mentioned its association with joint impairment (now known as arthropathic psoriasis) (1818, Jean-Louis Alibert) [1, 2]. The socio-economic impact of psoriasis has however been preserved [3], in the context of the generally severely impaired quality of life, as well as of forms refractory to treatment and frequent occurrence of comorbidities, accentuated by the fact that permanent cure for psoriasis is a goal yet to be accomplished.

Nowadays, some 2–3% of the population is affected, with too little dissimilarity between the two genders. From the perspective of race factors, studies conducted worldwide have shown 0.7% prevalence among individuals of African descent, relatively low frequency in native South-American populations as well as bimodal distribution as regards the age for its onset [4].

With regard to psoriasis-associated risks suggested by the results of epidemiological studies, the prevalence of various comorbidities and mortality seems rather high [5, 6]. Among the related comorbidities, mentioning due to psoriatic arthritis, chronic inflammatory intestinal disease and psychiatric and psychosocial disorders, as the most common; however, cardiovascular comorbidities (obesity, diabetes, dyslipidemia, hypertension as well as coronary disease) [7–10] have also more recently been shown to arise from psoriasis-induced metabolic changes. In this respect, research has found increased myocardial infarction risk for younger patients suffering from severe forms of psoriasis [11].

The clinical profile in psoriasis consists of erythematous and scaling lesions, distributed in various patterns and regions of the body. At the same time, a range of individual clinical phenotypes may be noted such as vulgar, pustular, inverted, erythrodermic and guttate. In 5–20% of the cases, psoriasis involves the joints and the nails [12]. A comparative look at premature onset or type I and type II or delayed onset psoriasis (arising between the ages of 50 and 60 or later), one should notice the former's more frequent family background of DR7 and HLA-Cw6 and the disease, as well as type I tendency to more significant dissemination and more frequent relapses [4, 12].

Psoriasis is known to be triggered and/or aggravated by such factors as trauma, drugs, infections, alcoholism and smoking [13, 14]. Given that psoriasis may not be yet cured, progress has mainly focused on suppression of the systemic inflammatory response and general disease signs, which are considered sufficient to allow symptom-free conditions for longer periods of time, as well as on development of therapies for accompanying diseases.

Not all has been fully clarified in relation to psoriasis pathogenesis mainly due to the involvement of complex factors of immunologic, environmental and genetic nature. Immune contribution to pathogenesis may be derived from the finding that former bone marrow transplant recipients from a donor with psoriasis also developed the disease; this has been further corroborated with the improvement of the disease observed subsequent to ablation followed by bone marrow transplant from psoriasis-free patients as well as by successful therapy using methotrexate, TNF- α inhibitors and cyclosporine [15–17].

Keratinocyte dysfunction is a result from tissue damage triggered by anomalous immunological response. This dysfunction can be observed in the more than 50 times increase of the

mitotic activity of basal keratinocytes in the psoriatic skin, resulting in reduced migration time (3–5 days as compared to the regular 28–30 days) from the basal to the corneal stratum [15, 18]. Histopathological examinations typically reveal parakeratosis, acanthosis, hyperkeratosis, accompanied by loss of the granular layer, elongation of epidermal ridges, vascular dilation, dermal-epidermal infiltrate and angiogenesis. In addition, which is a key for histopathological diagnosis, Munro's micro-abscesses are present, consisting of a sub-corneal aggregation of neutrophils [16, 19].

2. An overview of psoriasis therapy

Depending on the type and degree of severity as well as on the area of skin involved, age of the patient, costs, therapeutic management of psoriasis mainly consists of phototherapy, involving UV exposure of the skin, topical approaches and systemic medication but selection of the most effective treatment from the numerous therapeutic approaches is challenging.

Mainly consisting of application of ointments and creams to the skin, topical therapy is generally resorted to in cases of mild disease and formerly relied on use of keratolytic agents or emollients intended to help shed off or hydrate the skin. In keeping with further research developments, this type of treatment has increasingly targeted underlying proliferation of T-cell, therefore including vitamin D, coal tar, retinoids and topical calcineurin inhibitors.

For more severe forms, light-therapy and systemic treatments have been developed. Medication with systemic action administered orally or by injection includes the use of conventional drugs such as cyclosporine, acitretin, methotrexate and hydroxyurea, however associates with more prominent risk of serious adverse reactions, particularly for long-term treatment. One approach that has proved successful in improved and prompter effectiveness has consisted in combining all such therapies, achieving suppression of the disease and mitigation of adverse reactions. More recently, this has further been boosted by development of new, more targeted drug carrier systems. Development and increase of biological drugs and gene therapy have currently further supplemented therapeutic approaches with essentially ground-breaking new modalities, though none of them curative.

3. Medicinal products for systemic medications

3.1. Non-biological medication

3.1.1. Methotrexate – Overview

Methotrexate (MTX), a folic acid antagonist, has been used as non-biological medication in psoriasis therapy for longer than 30 years. Its use has proved successful in both treatment of psoriasis as such and of psoriatic arthritis and nail disease.

Though first used before introduction of routine conduct of randomized clinical trials and therefore still wanting in efficacy and safety data MTX is widely used in both mono- and combination dermatologic therapy predominantly for psoriatic arthritis and psoriasis, but also for dermatomyositis, sarcoidosis and pyoderma gangrenosum [17, 20, 21].

First authorised for psoriatic therapy in 1972, methotrexate was accordingly indicated, with no specification of the minimum body surface, for severe, refractory to topical therapy and phototherapy, and debilitating forms, therefore used in patients with functional disability arising from unresponsive scalp disease, palmoplantar disease or other severe, limited psoriasis forms.

Used in line with the standards established in guidelines published as early as 1972 and continually updated up to 1998 [22], MTX has proved successful in the treatment of pustular, plaque, guttate and erythrodermic psoriasis.

Furthermore, in 1988, MTX further received approval for the treatment of rheumatoid arthritis, the dedicated standards developed by the American College of Rheumatology (ACR), not requesting prior liver biopsy, which in fact were later eliminated from the guidelines for dermatologic use as well. However, the latter do not mention mandatory patient monitoring for possible liver toxicity resulting from methotrexate use [23]. At the same time, the issue of possible MTX liver toxicity is counteracted by such means as appropriate individual evaluation of patients' medical status, disease severity, quality of life, and psychological standing for proper selection and monitoring.

At the same time, MTX is used for cancer treatment, although in much larger dose than for dermatologic purposes:

Common approaches for MTX administration are as follows [24]:

- *Conventional low-dose therapy*, as follows:
 - dose: 15–50 mg/m² body surface area;
 - frequency: weekly, as one/several doses;
 - administration route: intramuscularly/intravenously.

Head and neck cancer:

- dose: 40–60 mg/m² body surface area;
- frequency: weekly, once;
- administration route: intravenous bolus injection.

- *Intermediate-dose therapy*, as follows:
 - dose: 100–1000 mg/m² body surface area;
 - frequency: single dose.

Cancer of the bladder, advanced squamous epithelial: intermediate dose, 100–200 mg/m².

- *High-dose therapy*, as follows:

- mostly in malignant diseases, e.g. acute lymphatic leukaemia, malignant lymphoma, metastatic choriocarcinoma, osteogenic sarcoma;
- dose: 1000 mg or more/m² body surface area;
- frequency: over a 24-hour period.

Folinic acid should be started at 10–15 mg (6–12 mg/m²), 12–24 hours after MTX therapy initiation.

Since 1998, a therapeutic approach of psoriasis has undergone remarkable changes, brought about by unprecedented expansion of basic and clinical research, leading to development of biologic agents such as alefacept, efalizumab, etanercept, infliximab, adalimumab and ustekinumab, which have all been approved for the treatment of psoriasis.

In comparison to biological drugs, even considering the costs of pre-treatment liver biopsy and blood monitoring, MTX is significantly less expensive, which explains why proof of intolerance or lack of responsiveness to methotrexate is a prerequisite for certain insurance companies.

However, considering the long-term aspect of psoriasis management and the associated issue of possible haematologic or hepatic toxicity with methotrexate, and notwithstanding reduced costs, targeted therapies allowed by biologic drugs are more viable alternative treatment options to methotrexate.

3.1.2. *Efficacy of methotrexate in the treatment of psoriasis*

MTX has been used effectively on patients suffering from widespread forms of psoriasis, unresponsive to phototherapy or topical therapy or disabling psoriasis [22].

The pharmacological action of MTX interferes with DNA synthesis and suppresses the immune system, resulting in notable slowing down the accumulation of dead skin cells.

Regarding actual administration, MTX is taken orally, in one weekly dose, either as a single dose or as three doses separated by 12 hours. Folic acid (a B vitamin) may also be administered as a concomitant supplement.

Generally, to reduce MTX toxicity, 5–10 mg folic acid weekly is recommended by most relevant reviews and guidelines; however, there is general agreement among them that 'the evidence base is insufficient to determine the optimum dose' and that there may be 'potential need for higher dosages, with the currently higher dosed methotrexate' [25].

Effects on the disease can be observed within several weeks from treatment initiation, as the condition of the skin starts to improve, full improvement to set in regularly in 2–3 months' time. To completely clear the disease, possible remaining plaques may be treated by topical application of other specific medication or UVB/PUVA phototherapy may be applied. This is also recommended when the MTX dose has to be reduced for toxicity reasons, combination with additional medication, e.g. a retinoid, is also an option.

Patients on MTX require close monitoring consisting of chest X-rays, regular blood tests or liver biopsy for more conclusive outcomes, as a result of possible damage to the liver and kidney functions or decrease of the body's capacity to produce white and red blood cells and platelets. Also, it should be borne in mind that MTX and specific metabolites intracellular accumulation leads to depletion of the folate store [26, 27].

The risk of adverse reactions may be dose dependent or vary with the route of administration (lower in parenteral administration) [28]. However, care should be exercised since doses under 15 mg/week may prove ineffective considering the therapeutic goal for disease control.

3.1.3. MTX contraindications and adverse reactions

Generally, MTX use is restricted by the risk of organ toxicity. Therefore, use of MTX for psoriasis is an absolute contraindication in:

- (a) Pregnancy or by women planning to become pregnant and their partners, because of MTX teratogenic effect. In fact, conception is to be avoided both during methotrexate therapy and for at least 3 months afterwards for males or for one ovulatory cycle for females;
- (b) Nursing;
- (c) Significant leukopenia, anaemia or thrombocytopenia.

In a number of cases, MTX may not be reasonably used for psoriasis treatment. Thus, MTX should be avoided for patients with [29]:

- (a) Active or recurrent hepatitis, cirrhosis or markedly deteriorated liver function, in the context of known liver toxicity potential of MTX; therefore, function tests are standard, as well as close monitoring in the case elevations are observed.

In the same respect, excessive alcohol consumption is also an issue—despite the scarcity of data to substantiate any definite limits for alcohol, which allows recommendations to vary from total prohibition of alcohol to permitted consumption of no more than drinks/day, liver damage associated with a history of alcoholism is undeniably problematic.

Also, in relation to MTX potential for liver toxicity, the drug is contraindicated in the case of other hepatotoxic drugs are used at the same time, which usually requires even closer liver function monitoring;

- (b) Abnormal kidney functioning; a significantly lower dose may be required, taking into account that the kidneys are the main excretion route for MTX (ca. 85%);
- (c) Active forms of infectious diseases, particularly chronic infections such as advanced HIV infection or active untreated tuberculosis, prone to exacerbation resulting from MTX immunosuppressive effects; therefore, in the case of patients on MTX developing an infection, the drug may be withheld temporarily.

The same may apply for immunosuppressed patients, but not to those using biologic therapies, for instance.

- (d) Obesity, with >30 body mass index;
- (e) Diabetes mellitus;
- (f) Recent vaccination, particularly for live vaccines;
- (g) Unreliable patient, which once more highlights the importance of psychological evaluation for patient selection for MTX therapy.

In the context of the above relative contraindications, cases may however arise when the benefits of MTX outweigh its inherent risks. Therefore, therapy decisions should be made for each individual patient, based on their specific status and background. For an obese patient with diabetes, for instance, who would benefit from short-term MTX therapy, the relative contraindication may be waived due to the short-term character of the therapy.

In MTX, there are three primary concerns for the physician, i.e. myelosuppression, hepatotoxicity and pulmonary fibrosis, as shown in a study conducted by the United Kingdom Committee on the Safety of Medicines on 164 possibly methotrexate-associated deaths reported during 1969–2004. Among these, 41% were attributable to myelosuppression, 18% to pulmonary fibrosis and only 0.5% to liver toxicity [30]. Though the risk of MTX-associated pulmonary fibrosis in the treatment of psoriasis is much lower than for rheumatoid arthritis (explaining why chest X-rays are not mandatory for routine baseline studies), development of pulmonary symptoms should be duly taken into account and pulmonary fibrosis should be considered [31, 32].

Hepato- and haematologic MTX effects may commonly manifest such as anorexia, nausea, stomatitis, malaise and fatigue, mainly right on administration. As shown by clinical experience, such manifestations may be avoided or alleviated by changing the administration route to subcutaneous or intramuscular injection or the time of administration to bedtime, supplementation of folates or dose-splitting.

Other adverse reactions have lately been identified and researched due to the more thorough study of the disease triggered by the introduction of biologic therapy and more sustained conduct of post-marketing surveillance studies, formerly obscured by the lack of closer scrutiny of MTX. Thus, such reactions as reactivation of hepatitis and tuberculosis and development of lymphoma (especially associated with the Epstein-Barr virus) have also been added to the list of potential toxicities [33–36].

In addition, as reported from a recent study conducted in the general population, a 50% increased risk of malignancy could also be observed, more precisely, the respective rise related to a fivefold increase in non-Hodgkin lymphoma, a threefold increase in melanoma and an almost threefold increase in lung cancer [37], which requires mandatory increased physician care for the unexpected in patients on immunosuppressive therapy in general.

Unexpected benefits are also possible in MTX side effects, such as its demonstrated protective effect as anti-inflammatory medication against cardiovascular disease in certain patients [38, 39], which is important for the overall benefit/risk balance of MTX.

3.1.4. MTX haematologic toxicity

In respect of haematologic toxicity, the main recognised risk factors of MTX therapy are renal impairment, advanced age, absence of folate supplementation, drug interactions as well as medication errors. Given that most part of the data on myelosuppression has been derived from patients with rheumatoid arthritis, the relative risk of myelosuppression in MTX treatment for psoriasis may only be inferred. Current literature suggests that, in properly monitored psoriasis patients and in the absence of risk factors for haematologic toxicity, cases of clinically significant myelosuppression only rarely occur. Even with low-dose weekly MTX, however, rare, pancytopenia and significant cytopenia are a permanent possibility in the presence haematologic risk factors, impaired renal function or even medication errors [40, 41]. This once again speaks for the importance of regular monitoring of haematologic toxicity by complete blood cell counts. For patients without risk factors, the monitoring routine should consist of a first repeat laboratory check within a 2-week period. Taking into account the possibility of pancytopenia in 4–6 weeks after increase of the MTX dose, as reported in some cases, monitoring should become more frequent in dose changes; in fact, according to some experts' opinion, complete blood cell counts should be best undertaken at least every 4 weeks [29]. Overtime and in patients with consistently stable conditions, the frequency of laboratory monitoring may decrease to 1–3-month intervals.

Given the higher significant renal impairment risk even at single weekly MTX doses, the glomerular filtration rate should be calculated even for patients with normal blood creatinine and urea nitrogen levels but at renal insufficiency risk because of age or decreased muscle mass considerations. In patients with known or at risk of impaired kidney function, careful monitoring should be a permanent concern and second doses or any dose increases should only be given after prior laboratory checks.

As medication interactions are an important source of adverse effects as well, in order to avoid error, patients should routinely be instructed to the proper use of MTX therapy.

3.1.5. MTX hepatotoxicity

In respect of MTX hepatotoxicity, the issue of liver biopsy has remained a subject of debate among physicians involved in MTX therapies for both rheumatoid arthritis and psoriasis. The opinion prevails among rheumatologists that, particularly in healthy patients, liver biopsy is not necessary [42]. To that stricter dermatology guidelines argue that hepatic toxicity is greater in psoriasis patients, partly relying on the confirmed higher incidence of rheumatoid arthritis among women, less in the habit of alcohol consumption and therefore at liver damage risk than men. On the other hand, as confirmed by recently published updates, higher liver damage incidence for psoriasis patients results from common risk factors such as obesity, diabetes, alcoholism as well as previous exposure to hepatitis and liver toxins [42–45].

This is corroborated with histopathologic features of MTX-induced liver toxicity, which are roughly similar to the liver histology pattern common in hyperlipidemic, obese or diabetic patients or to non-alcoholic steatohepatitis (NASH). Clinical practice has in fact shown that, compared to no-risk psoriasis patients, NASH risk factors likely aggravate pre-existing NASH and eventually contribute to development of liver fibrosis even at lower MTX cumulative doses for psoriasis therapy. Such risk factors may represent inherent psoriatic patient phenotypes increasing hepatotoxicity risk. Provided controls of such confounding variables were introduced in studies conducted, MTX-associated liver injury rate in psoriatic patients would probably be roughly similar to that encountered in rheumatoid arthritis patients [43, 46, 47]. All the above come to highlight that the necessity of the liver biopsy is a matter of individual patient condition and medical background and should be judged on a case-by-case ground.

As current guideline standards recommend for practice, based on their risk factors for liver injury, patients intended for MTX therapy should be divided into two groups, i.e. no-risk versus risk patients. In the former group, the risk of fibrosis is lower and similar to rheumatoid arthritis, which makes them eligible for application of ACR criteria for MTX monitoring (i.e. liver function evaluation every 1–3 months and liver biopsy in the case of elevation of 5–9 serum AST levels over a 12-month period or of serum albumin decline below the normal range against normal nutritional status and well-controlled disease), a practice-validated routine schedule allowing for safe reduction of biopsies performed [48].

According to other recent data, the first liver biopsy in patients without pre-existing hepatotoxicity risk factors should be performed on use of a 3.5–4.0 g in place of the 1.0–1.5 g cumulative MTX, routinely recommended for pre-existing risk factors [43, 49, 50]. In low-risk patients on MTX, for normal values found in history of liver conditions, physical examination and liver laboratory tests, the decision whether or not to perform liver biopsies should be individual and rely on relative risk evaluation. Further monitoring options for patients on 3.5–4.0 g cumulative dose consist of application of ACR guidelines and continued monitoring with no biopsy, conduct of a first biopsy at the 3.5–4.0-g level, or stopping MTX altogether or, if feasible, switching the therapy to some alternative treatment, if possible. In the case of normal results in the first biopsy, further liver biopsies in low-risk patients are conducted in line with the ACR guidelines-recommended timeframes.

It is generally agreed that management of patients with one or several hepatic fibrosis risk factors should be conducted in line stricter guidelines. Therefore, the presence of significant risk factors should first of all trigger consideration of the feasibility of therapy consisting of a different systemic agent. Next, a risk/benefit evaluation should be undertaken for each individual risk patient, to weigh the benefits against the risks of MTX therapy.

In the case of likely MTX benefits exceeding possible risks, liver biopsy is advisable on inception of the therapy. Biopsy results permitting, MTX may be started although, in a small number of patients, it would likely stop in 2–6 months after initiation mostly because of adverse effects or lack of clinical efficacy. In light of this possibility, the pre-treatment liver biopsy may be postponed until after this 'trial' period, as there are no data indicative of clinically significant liver disease triggered by short or several-month MTX treatment. In the case of anticipated long-term therapy or for patients with persistent significant abnormalities in laboratory

liver values, the initial biopsy is recommendable. In patients with acknowledged risk factors for liver disease, the liver biopsy should be repeated at a 1.0–1.5 g cumulative dose. Higher risk patients also require repeated biopsy with every MTX additional 1.0–1.5 g. However, as liver biopsy is not without risks, the procedure may not be appropriate or may be referred to another time in case, for the individual in question, risks of the biopsy *per se* outweigh the benefits; anyway, the risk of advanced fibrosis and that of liver biopsy complications should be carefully balanced.

However, although an important matter in itself, there is no screening tool for liver fibrosis available, allowing for relatively safe and effective decision on whether or not to use liver biopsy in the management of patients on MTX or at least decrease its need. Various other means have been tested in that respect, such as ultrasonographic tests and radiographic imaging techniques, but these have been mostly unsuccessful. More recently, measurement of a potential marker has been also tried, i.e. the amino-terminal peptide of procollagen III (PIIINP), and comparative results have shown a sevenfold decrease in the number of biopsies in the group managed with application of the Manchester PIIINP guidelines as compared to the group for which the 1998 American Academy of Dermatology guidelines were applied [51]. Such results were later supported by an additional study showing the possibility of complete biopsy exclusion provided the PIIINP values remained stable [52]. Accordingly, this test is used as a monitoring tool for hepatic fibrosis by most practicing dermatologists in the UK and formal testing is currently put on hold in the US. One other additional aspect highlighted by the British study on PIIINP is the difference in characteristics among commercially available PIIINP kits [53, 54].

Lately, the potential MTX-associated hepatic fibrosis and cirrhosis have been shown to be considerably less aggressive than initially estimated [55, 56]. At the same time, there is an observable tendency for adverse events to mostly occur in patients with internal abnormalities associated with other diseases. More specifically, risks such as gallbladder perforation, hemoperitoneum subcapsular haemorrhage and pneumothorax are lower in psoriatic patients than in those with other diseases [57].

3.2. Therapies involving biological and biosimilars

In the same way as for rheumatoid arthritis, development of biologicals has been a groundbreaking event for the treatment of psoriasis, leading to unprecedented success in therapeutic approach of moderate-to-severe forms of psoriasis and psoriatic arthritis. In that respect, even if not considered first-line treatments, biologic agents such as etanercept, adalimumab, infliximab and ustekinumab have been approved as second-line therapies for psoriasis, whereas golimumab has been approved for psoriatic arthritis therapy.

Clinical practice with biologicals has revealed their higher efficacy and tolerability in comparison to traditional systemic therapies [58], even in cases of refractory disease and expressly indicated for use in the so-called high-need patients, unresponsive or intolerant to all other available and approved systemic agents, MTX and cyclosporine included, or who cannot possibly use such conventional systemic agents for reason of pre-existing disease [59].

In addition, biologicals do not generally carry the same toxicity burden of toxic chemical or pharmacological adverse effects. Most related side effects are due to the specific biological properties of a given preparation, and result from neutralization of the biological activity of their target molecules, such as TNF- α or IL-12/IL-23.

Psoriasis treatment can now rely on agents such as the TNF- α antagonist etanercept, adalimumab and infliximab, and on ustekinumab, a p40-antagonist. An additional issue brought about by immunological properties of the novel biological therapies is the occasional need to switch between therapies because of immunological side effects such as severe local reactions or secondary loss of activity [60].

In fact, developments have been both rapid and uneven: on the one hand, biologicals mentioned above are currently standard for a certain group of psoriatic patients, and specific guidelines have been developed [60, 61] whereas, on the other hand, in spite of their undeniable usefulness, biological drugs are yet not in wide use for psoriasis treatment [61], partly because of practitioner's lack of awareness about their use for psoriasis and more importantly because of their comparative high costs.

This issue of cost effectiveness (the same benefit obtained with lower treatment costs) has prompted development of biosimilar alternatives following expiry of patents for biologicals; thus, in the context of a cost minimisation process, the appropriate products would be determined by price only [59]. Such so-called biosimilars as erythropoietin preparations and growth hormones have been developed in recent years for use in certain indications [62, 63]. In fact, an increasing range of pharmaceutical companies, mostly Asian, have already developed biosimilar drugs relying on evidence derived from controlled clinical trials [64].

In biosimilars, the therapeutic protein is obtained by recombinant technology, and its structure is similar to that of the original biological product ('the reference drug'); this accounts for their very name—'biosimilars'. In addition, the pharmacological effects of the biosimilar as well as its mechanism of action are presumed identical to those of the reference [65].

If compared to drugs developed by chemical synthesis, the molecular weight of biosimilars is higher and their molecular structure is very complex. Although identical to amino acid sequence, their tertiary and quaternary structures may be heterogeneous, impacting their respective efficacy and safety profiles. Although similar in concept, biosimilars as copies of biologicals and generics as copies of chemically synthesized drugs must be treated in the same way, a fact clearly recognised by regulatory measures for assessment of preclinical data of both the EMA and the FDA.

In the same way as for generics and original drugs, since their very proposal as alternatives, the issue has been raised with regard to the extent that a structurally similar imitation of a drug could actually present identical efficacy and safety as the original [66]. It has been argued that variations in manufacturing processes may result in alterations of clinically relevant properties, likely to affect the finished product and subsequently monoclonal antibodies. But even if successful in part only, biosimilars would lead to significant reduction in drug costs as well as to a re-structuring of the pharmaceutical market.

The limitations of biosimilars would thus consist of possibly diminished reduced efficacy and higher risk potential from new side effects arising from such manufacturing variations [67]. Critical assessment of functional differences between biosimilars and their reference biological drug is essential for successful therapy and treatment safety.

Biosimilars display several biological characteristics, giving rise to specific consequences for clinical use. In biologicals and accordingly in biosimilars as well, proteins are formed by protein folding, resulting in a complex three-dimensional structure [65]. The biotechnological manufacturing process may induce batch-to-batch variations in the tertiary and quaternary structure even within a single production line [53, 65]. In addition, change in conditions at the manufacturing site or even switch from one site to another have often negatively impacted the quality and stability of biological drugs (according to [68]). The case has become known of the transfer to a company's new facility of the manufacture of efalizumab, a biological drug specifically designed for psoriasis treatment, which induced differences of such a scale in biological characteristics that prompted an FDA request for new phase III study meant to assess and reconfirm bioequivalence [69].

Such clinically relevant variations in manufacture of a biosimilar have also been reported for erythropoietin, for instance, with the alteration of protein characteristics, resulting from different properties of ionic bonding [70].

Respective risk of the modified therapeutic effect is even greater in the case of biosimilars introduced as a *de novo* production line.

However, the reverse is also true, and biosimilars may have improved properties in comparison to the original, and this is the case of the so-called biobetters, provided improvements are subjected to systematic research and implementation.

With regard to the ability of biological drugs to elicit an intended or unintended immunological response (immunogenicity), this is of special importance for this type of medicines, due to their marked immunogenic capacity resulting from their molecular structure (protein, polypeptide) [71]. Typically, the immunogenicity and biological functions of proteins are a result of both covalent bonds and their native tertiary structure [72]. From the perspective of biosimilars, though not yet fully demonstrated, it cannot reasonably be assumed that alterations to the tertiary structure, however structurally minimal but significant as regards function, are unable to determine changes in immune responses, giving rise to autoimmune or allergic complications [70, 72–74]. On the other hand, the possibility also exists for the biological drug to prove excessively effective or become inactivated form of an immune reaction.

In the context of the high specificity of processes for the manufacturing of biologicals, they cannot possibly be fully replicated for manufacture of their biosimilars. The differences may arise from various sources, such as selection of production site as well as of cell lines, the manner of cell nutrition, fermentation conditions, the production temperature and environment, etc. [66] and they can each alter the recombinant drug's effectiveness, stability and tolerability [75, 76]. Even when subjected to close monitoring and careful compliance with strict quality in the production process, variability in product quality (i.e. the integrity of the finished product) cannot be routinely excluded [77].

In addition, variability of biological activity may also derive from its marked sensitivity to such environmental physical conditions as phases, temperature or shearing forces, to changes in the manufacturing process resulting in variable enzyme activity as well as to formulation changes [78]. Under the circumstances, it may reasonably be assumed that the drug's safety may also undergo some degree of influence and safety studies are therefore needed to test their behaviour in everyday use [79, 80].

In order to specifically determine the implications for clinical practice with biosimilars in psoriasis treatment, longitudinal studies are necessary, which has prompted both dermatologists and rheumatologists to require study of biosimilars in long-term registries as per their indications for use [68, 81]. An initiative in the respect is the PsoBest, conducted in Germany [82] as well as worldwide, with comparable registries [83, 84].

To counteract the possibility of diminished reduced efficacy and higher risk potential from new side effects in biosimilars, as early as 2004, the European Medicines Agency (EMA), followed by the U.S. Food and Drug Administration (FDA) developed legal and regulatory requirements (the consolidated Directive 2001/83/EC) and guidelines applicable to their development, evaluation and marketing, based on submission of preclinical data and clinical characteristics. As the time for patent expiry for biological drugs approved for psoriasis treatment draws nearer (e.g. the U.S. patents for etanercept was issued in 2012, for adalimumab in 2016 and infliximab in 2014), the market will be open for biosimilars, which requires urgent clarification of actual meaning and implications for healthcare regulation in general and for dermatology in particular. Therefore, a description is useful related to future introduction of biosimilars in the treatment of psoriasis and psoriatic arthritis, making use of current regulatory requirements and published data.

The same as for conventional medication, EU regulations require authorisation of biologicals and biosimilars. Centrally, scientific assessment is conducted by the European Agency's Committee for Medicinal Products for Human Use (CHMP) [85]; assessment may result in a recommendation on whether the medicine should be marketed, adopted by the EMA and transmitted to the European Commission which grants a marketing authorisation, applicable to all EU member states.

However, when it comes the evaluation of clinical bioequivalence, the EMA and the FDA have different perspectives: the EMA only requires evidence of pharmacodynamic and pharmacokinetic equivalence, with additional evidence of clinical bioequivalence from randomized clinical studies being necessary in uncertain cases only [68], whereas the FDA insists on bioequivalence being supported by clear factual information, resulting from clinical studies.

The EMA and FDA approaches for post-marketing surveillance are similar in that both require conduct of non-interventional safety trials after marketing.

EMA guidelines have been developed in relation to the quality of biologicals, stating preclinical and clinical requirements, as well as product specifications [76–88]. According to EMA guidelines, biosimilars should be deemed specifically different from generics and use of approval procedures for generics is prohibited in relation to biosimilars. Further provisions regard the manufacturer's obligation to conduct clinical studies [89] seeking to demonstrated

similarity of quality, safety and efficacy between the biosimilar and its biological reference drug. The same similarity must apply to the formulation, concentration and mode of administration of the therapeutic substance. Such data are derived for assessment purposes from preclinical experiments, both *in vitro* and *in vivo*, as well as from clinical studies conducted on patients or healthy volunteers; however, the amount of data required for biosimilars is less extensive than for the original biological.

At the same time, the biosimilar manufacturer is required to submit a risk management plan, focusing on safety specifications as well as a pharmacovigilance plan and a risk minimisation plan.

A further regulatory request for biosimilars is that they should allow for clear identification, for instance by use of distinct brand names or non-proprietary names, which allow for clear documentation, particularly in what concerns reports of potential adverse reactions and side effects.

The EMA's appointed (co)-rapporteurs undertake a scientific assessment of the documentation submitted in support of the application for biosimilar authorisation, on a case-by-case basis. Positive assessment opinion results in grant of a marketing authorisation by the European Commission.

Provided certain conditions are met, the EMA allows for extrapolation of initially approved clinical indications for which they can provide evidence. This is of particular importance for psoriasis, which, because of the widely varying characteristics of the disease, patient features and similarities of risk profiles between psoriasis and rheumatoid arthritis, for instance, requires critical evaluation of claims of analogies between indications [81, 90, 91].

Exchangeability and substitution are also of importance with regard to the biological reference drug-biosimilar relation; exchangeability is the term used to refer to the possibility of replacement based on medicinal and pharmaceutical characteristics between a drug developed for a specific indication and a different substance with identical effects. This is only feasible when the substitute drug has same quality, safety and efficacy features as the substituted one. In pharmaceutical practice in Germany, for instance, drugs may be substituted if the substitute has been approved in relation to reference product, and no difference could be established with regard to original substance or their manufacturing process. In that context, taking into account the differences in manufacturing processes of biosimilars and their resulting immunological and pharmacological characteristics, identity with the reference in terms of active ingredients may be ruled out [92].

Currently, the clinical consequences of repeated substitutions with biosimilars, either between themselves or for a biological, are only reviewed in few clinical studies [92]. This has prompted the EMA recommendation that the decision as to which of the two, the original biological drug or its biosimilar, should be given should be the sole choice of the treating physician. This has been preceded by measures of national authorities such as the Drug Commission of the German Medical Association, which has issued a warning against substitution of biotechnological drugs for one another in the absence of medical reviews. Substitution of an original biological product with its biosimilars is only possible on explicit request by the patient's physician.

Also pertaining to substitution and exchangeability, one very important aspect is that, particularly where patients with chronic disease and clear immunological origins such as psoriasis are involved, uncontrolled product switching and the so-called 'product hopping' should be avoided.

With regard to the pharmacovigilance aspects of biologicals and biosimilars, their total range of immunogenicity and associated reactions remains yet to be researched and described: data from clinical studies and trials need to be complemented with information from actual healthcare practice [93]. The capacity of biosimilars to induce immune responses needs to be studied after their actual placement on the market and the same pharmacovigilance provisions should apply to biosimilars as to their reference. This obligation requires conduct of post-marketing studies, mainly designed as controlled patient registries. In that respect, the EMA has also developed a comprehensive post-marketing pharmacovigilance program applicable to biosimilars, consisting of performance of a post-marketing safety study and implementation of a risk management plan, including:

- Spontaneous reporting of potential side effects associated with use of a biosimilar after their reporting by patients themselves or healthcare professionals;
- Preparation of Periodic Safety Update Reports (PSURs);
- Preparation of post-authorisation safety studies (PASS) (also known as phase IV studies) [94].

Pricing issues are also relevant for biosimilars, which, although considered less costly in comparison to their biopharmaceutical reference, because of the considerable research and development financial investments (currently, 80–120 million Euros), to which costs of biotechnological production sites must be added, do not in fact bring about a very great difference as price is concerned (not exceeding 20–25% less than the biopharmaceutical reference).

All the aspects considered, introduction of biosimilars into therapy, psoriasis treatment included, will undergo constant increase after patent expiry for original. The process will however increase the need for information from healthcare professionals, carers and patients alike.

4. MTX therapeutic benefits versus toxicology emergencies

In psoriasis therapy, low MTX doses are rarely associated with toxicity, and in most cases this only occurs because of non-compliance with the recommended guidelines [95].

However, the risk of MTX toxicity increases when additional MTX is administered sooner than provided for by the routine planned weekly dose [96], as, for instance, in the case of out of self-administration outside therapeutic protocol of a higher, consecutive dose, acting as precipitating factor.

MTX toxicity may be observed by its effects on the skin (ulcerations), the gastrointestinal mucosa, as well as at liver, kidney and bone marrow levels. Limitation of toxicity-related skin

ulcerations to psoriatic plaques is likely the result of higher MTX uptake by the hyperproliferative psoriatic plaques as compared to the normal skin. The influence of toxicity may be assessed by both evaluation of change of membrane fluidity at the cellular level [97, 98], as well as *in vivo*, by confocal microscopy [99].

MTX-induced pancytopenia may occur in renally impaired patients as well as in cases of folic acid deficiency, infection and hypoalbuminemia but also as a result of concomitant drug use (e.g. trimethoprim) and advanced age [100].

Additional features of MTX toxicity are mucositis and myelosuppression, the likely cause of the latter being advanced age [101], concomitant NSAID use and careless use of the prescribed MTX dose; in other cases, this may be a result of renal dysfunction not identified prior to treatment initiation. However, inadvertent MTX dosage is the major contributory factor for MTX toxicity found in clinical practice, which strongly speaks for mandatory avoidance of MTX self-administration and appropriate patient instruction in that respect as well against combination of MTX with other drug without prior medical counselling.

MTX toxicity potential may be enhanced by use of generally renotoxic drugs which either decrease MTX renal elimination (e.g. cyclosporine, aminoglycosides, nonsteroidal anti-inflammatory agents, probenecid, sulfonamides, salicylates, colchicines, penicillins and cisplatin) or induce MTX displacement from protein binding sites in the plasma (as is the case of salicylates, sulfonamides, probenecid, phenytoin, barbiturates, sulfonyleureas, retinoids and tetracyclines). Use of NSAID for joint pain can contribute to MTX toxicity.

Methods for MTX quantification also exist, as both a parent compound and mostly as MTX polyglutamate forms, responsible for its effect [102, 103].

To avoid toxicity, over-the-counter availability of MTX should be prohibited.

5. Discussion

Development of biological medicines has brought about new therapeutic options for psoriasis and other inflammatory diseases, which have proved successful in the therapy of moderate-to-severe and severe forms of plaque psoriasis alike.

Although giving rise as novel therapeutic agents to concerns related to their efficacy and safety, innovative pharmacobiologicals such as etanercept, adalimumab, infliximab, ixekizumab, ustekinumab and secukinumab, to mention a few, clinical practice has proved their short- and long-term efficacy and remarkable tolerability.

The process is currently replicated with regard to emerging biosimilars, developed for treatment of the same conditions as their original reference. Suspicions as to their safety and efficacy should be lifted by the undeniable outcomes derived from in-depth clinical trials already conducted and clinicians should more resolutely make use of their demonstrated capacities.

In an overall context of unmatched medical and pharmacological development, mainly characterised by the uniquely fast pace of research and findings in the area of biologicals and biosimilars, these currently play a remarkable role in advanced medicine. However, this has also raised a challenge for both international researchers, developers, manufacturers and for other drug-related regulatory fields such as the development of standards and pharmacovigilance, as the most important. This is further enforced by the expectation that, at least in Europe, biosimilars would lead to 15–30% cost reduction in use of biological therapeutic agents.

With regard to the therapeutic benefits-toxicological emergencies ratio particularly in psoriatic patients, there is a common concern related to possible association of MTX therapy with toxicity in various forms, of which some are serious and, in rare cases, may even include patient death.

Because of their implication for clinical practice, two aspects should be particularly outlined in relation to MTX toxicity: firstly, there is their potential to manifest at any time during the treatment, which calls for constant monitoring; secondly, the importance of the MTX dose or the dosing frequency for determining the risk for both toxicity and its severity.

MTX-induced toxic effects of special concern are severe skin reactions, hepatotoxicity (with both acute and chronic forms, with liver fibrosis and cirrhosis), acute haematological toxicity, lymphoproliferative disorders and severe opportunistic infections, lung disease and serious gastrointestinal toxicity.

Given this relatively high-risk context, further complicated by the additional threat posed by the potential for serious cumulative toxicity, MTX therapy is generally to be used mainly for patients with severe psoriasis, whose quality of life is seriously affected by their disease as well as for cases where proper disease control cannot be accomplished by use of topical therapies. As a further minimisation measure, MTX dose reductions and off-treatment periods should be applied whenever possible.

Undeniably, a therapeutic advantage due to relatively low costs of therapy complemented by ease of oral administration, in the presence of potential to achieve reasonable safety and tolerance, use of MTX has to be considered against its serious toxicity potential, which may be kept under control by careful patient selection and individual assessment of the benefit-risk balance for each psoriasis patient, accompanied by routine monitoring and strict compliance with monitoring guidelines.

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Author details

Carolina Negrei^{1*} and Daniel Boda²

*Address all correspondence to: carolina.negrei@outlook.com

1 Department of Toxicology, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

2 Centre of Excellence in Dermato-Oncology, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

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